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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/530,747	10/23/2000	Christoph Kessler	4817/OR	5088

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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,747	KESSLER ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12-2002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to Applicant's amendment and response to office action, filed April 1, 2003. Claim 1 has been amended as well as the specification and no claims have been canceled or added. Claims 1-9 are still pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. All rejections not reiterated herein are hereby withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Priority

Acknowledgement of claim to foreign priority of German Applications, 197 48 690.8, filed 11/04/1997 and 198 14 001.0 filed, 03/28/1998under 35 U.S.C. 119(a)-(d) has been made, however applicant should note that the certified translation of these foreign priority documents have not yet been received and as a result the claim to foreign priority under the same has not yet been granted.

Response to Arguments

In the response filed April 1, 2003, Applicants traverse the previous 112 2nd rejections by stating that the claims have been amended, and the new claims obviate the indefiniteness problem of claims 1-9 in their comments "A" and "B" on page 6 of their response. However, the claims remain indefinite for the following reasons as stated below.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-9 are indefinite over the recitation of "wherein the amplificates have a length of 75 nucleotides or less, and the sequences located between the binding sequences A and C contains no nucleotides that do not belong to a sequence region E of the amplificate that is bound by binding sequence D of the probe" in Claim 1(b). First, claim 1 lacks antecedent basis for this limitation of the sequences between the "binding sequence A". In part (a) of claim 1, only a "binding sequence A' "is mentioned, a reference is not made to a "binding sequence A." Applicant should clarify between which two sequences and on what strand these "sequences located between the binding sequences" are located.

B. Claims 1-9 are further indefinite over the recitation of "contains no nucleotides that do not belong to a sequence region E of the amplificate that is bound by binding sequence D of the probe". Since it is not clear what the sequences located between the binding sequences A and C are, as noted in the rejection of section "A." above, it is further indefinite to qualify their composition, especially with a double negative. Applicant should clarify the composition of the sequences located between the binding sequences.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Livak et al. (US Patent 6,154,707).

Livak et al. teach a method for the detection of a nucleic acid comprising: producing a plurality of amplificates of a section of the nucleic acid by amplifying said section of nucleic acid with two primers, one primer binding to the Watson strand, and the other binding to the Crick strand(See FIG. 1A), the primers do not overlap. The reference further teaches this 5' nuclease assay that employs oligonucleotide probes labeled with at least one fluorescer and at least one quencher that hybridize between and avoid overlap with, the primers(FIG 1A-1D). Prior to cleavage of the probe, the at least one fluorescer excites the quencher(s) rather than producing a detectable fluorescence emission. The oligonucleotide probe hybridizes to a target oligonucleotide sequence for amplification in PCR or similar amplification reactions. The 5' to 3' nuclease activity of the polymerase used to catalyze the amplification of the target sequence serves to cleave the probe, thereby causing at least one fluorescer and/or a change in fluorescence of the quencher due to the oligonucleotide probe being digested is used to indicate the amplification of the target oligonucleotide sequence. The reference further teaches this method wherein at least one binding sequence, at least one primer, at least one probe, and

wherein two primers are not specific for the nucleic acid to be detected in that it teaches; it is often desirable to analyze a sample containing multiple different targets using a different spectrally resolvable species for each target(Col. 2), each set of oligonucleotide probes includes two or more probes which are complementary to different members of a set(Col.3-4), and at least one primer capable of hybridizing to the sample of DNA and amplifying the at least two different allelic sites in the presence of two or more sets of allelic oligonucleotide probes(Col 4). Lastly, the reference teaches that the operation of the 5' nuclease assay has been found to improve as the length of the sequence being amplified decreases. Consistent and predictable results have been routinely obtained for amplicons as short as 50 bp and as long as 150 bp(Col.17). Furthermore, the reference includes the teaching of nucleotides which are complementary to A, G, C and T to be used in the amplification(Col. 8).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livak et al.(US Patent 5,538,848) in view of Khan et al.(US Patent 5,948,648).

The reference teaches a method for the detection of a nucleic acid comprising:

(a) producing a plurality of amplificates of a section of the nucleic acid by amplifying said section of nucleic acid with two primers, one of which binds to a first binding sequence A' of one strand of the nucleic acid, wherein said binding sequence A' is essentially complementary

to a sequence A, located on the other strand of the nucleic acid, and the other primer binds to a second binding sequence C, which is located in the 3' direction from A and does not overlap A, in the presence of a probe having a binding sequence D which binds to a third sequence B located between the sequences A and C or to the complement thereof, wherein the probe contains a reporter group and a quencher group, using a polymerase having 5, nuclease activity; Other claims are drawn to the probe sequence not overlapping that of the primers, the binding sequences not being specific for the nucleic acid to be detected, the primer being less than 61 nucleotides in length, the probe being labeled with a fluorescent quencher as well as a fluorescent dye, and to the nucleotides being complementary to A, G, C, and T. Livak et al. teach "A method is provided for monitoring the progress of nucleic acid amplifications that rely on a nucleic acid polymerase having 5' to 3' exonuclease activity, which also has 5' nuclease activity. An important feature of the method is providing an oligonucleotide probe having a reporter molecule and a quencher molecule at either end such that the quencher molecule substantially quenches any fluorescence from the reporter whenever the oligonucleotide probe is in a single stranded state and such that the reporter is substantially unquenched whenever the oligonucleotide probe is in a double stranded state hybridized to a target polynucleotide." (Abstract). Livak at al. also teach "The binding site of the oligonucleotide probe is located between the PCR primers used to amplify the target polynucleotide." (Col. 4, line 20). In other words, Livak et al. teach two primers and a probe which hybridizes in between the primers, and contains a reporter and a quencher molecule.

Livak does not teach that the amplificate is less than 75, or 61, nucleotides in length.

However, Khan et al. teach a method for performing a primer extension reaction comprising the steps of providing a template nucleic acid, annealing an oligonucleotide primer to a portion of the template nucleic acid for forming a primer-template hybrid, and adding primer-extension reagents to the primer-template hybrid for extending the primer, where the primer extension reagent includes a nucleoside/tide compound(Col. 3). The method taught includes the polymerase chain reaction wherein amplificates of "less than about 50 nucleotides in length, such products including both the first and second dyes" were formed(Col.17 lines 53-54). The reference further teaches this production of short amplificates to be the result of using too much dideoxy terminator, that is taught in the patent. Subsequent to the polymerization reaction, a set of polynucleotide probes will be bound to the created fragments in a sequence-dependent manner. In a preferred embodiment of the reference, multiple classes of polynucleotides are separated or hybridized simultaneously and the different classes are distinguished by spectrally resolvable labels(Col. 11).

Therefore, It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the teachings of Livak in view of Khan. Khan's teaching of using a nucleoside/tide compound and its ability to produce small amplificates, labeled with a first and second dye, on the order of less than 50 nucleotides would be added to the teaching of Livak et al. for the expected benefit of producing and subsequent detection of amplicons 61 bp or less.

4. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livak et al.(US Patent 5,538,848) in view of Walker et al.(PNAS Vol.89, pp. 392-396).

The reference teaches a method for the detection of a nucleic acid comprising:

(a) producing a plurality of amplificates of a section of the nucleic acid by amplifying said section of nucleic acid with two primers, one of which binds to a first binding sequence A' of one strand of the nucleic acid, wherein said binding sequence A' is essentially complementary to a sequence A, located on the other strand of the nucleic acid, and the other primer binds to a second binding sequence C, which is located in the 3' direction from A and does not overlap A, in the presence of a probe having a binding sequence D which binds to a third sequence B located between the sequences A and C or to the complement thereof, wherein the probe contains a reporter group and a quencher group, using a polymerase having 5, nuclease activity; Other claims are drawn to the probe sequence not overlapping that of the primers, the binding sequences not being specific for the nucleic acid to be detected, the primer being less than 61 nucleotides in length, the probe being labeled with a fluorescent quencher as well as a fluorescent dye, and to the nucleotides being complementary to A, G, C, and T. Livak et al. teach "A method is provided for monitoring the progress of nucleic acid amplifications that rely on a nucleic acid polymerase having 5' to 3' exonuclease activity, which also has 5' nuclease activity. An important feature of the method is providing an oligonucleotide probe having a reporter molecule and a quencher molecule at either end such that the quencher molecule substantially quenches any fluorescence from the reporter whenever the oligonucleotide probe is in a single stranded state and such that the reporter is substantially unquenched whenever the oligonucleotide probe is in a double stranded state hybridized to a target polynucleotide." (Abstract). Livak at al. also teach "The binding site of the oligonucleotide probe is located between the PCR primers used to amplify the target polynucleotide." (Col. 4, line 20). In other

words, Livak et al. teach two primers and a probe which hybridizes in between the primers, and contains a reporter and a quencher molecule.

Livak does not teach that the amplificate is less than 75, or 61, nucleotides in length. However, Walker et al. teaches an isothermal amplification of DNA by a DNA polymerase system. The reference further teaches the detection of a 47-bp amplified target DNA fragment resulting from this amplification step. The Walker reference teaches using a restriction enzyme to cut the PCR product prior to its detection to allow for the detection of a small resulting amplificate(Pg. 393).

Therefore, It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the teachings of Livak in view of Walker, as the addition of restriction enzyme sites to the sequence of primers is well known in the art and would have been obvious to the practitioner of the Livak method in their attempt to detect small amplicons of 61 bp or less.

Claim Rejections - 35 USC § 112

--New Matter--

5. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "A being replaced with A'" and "C' being replaced by C" in claim 1 and throughout the specification appears to represent new

matter. Applicant points the examiner to page 44, line 16 to page 45, line 5 and Figs 2, 6 and 7 to find the support for the amended Claim 1. However, no specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

6/5/2003

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER